DATA EVALUATION RECORD

ETHABOXAM (LGC-30473)

SUBCHRONIC ORAL TOXICITY: DOG [OPPTS 870.3150 (§82-1b)]
MRID 46387803

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1801 Bell Street
Arlington, VA 22202

Prepared by

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Task Order No. 103-2005

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DATA EVALUATION RECORD

STUDY TYPE: Subchronic Oral Toxicity - Dog; OPPTS 870.3150 [§82-1b]; OECD 409.

PC CODE: 090205 **DP BARCODE**: D313732

TEST MATERIAL (PURITY): Ethaboxam (LGC-30473, 99% a.i.)

SYNONYMS: *(RS)-N*-(α-cyano-2-thenyl)-4-ethyl-2-(ethylamino)-1,3-thiazole-5- carboxamide

CITATION: Gardner, T. (2001) LGC-30473: Toxicity study by oral capsule administration to beagle dogs for 13 weeks. Huntingdon Life Sciences Ltd, Woolley Road, Alconbury, Huntingdon, Cambridgeshire, PE28 4HS, England. May 3, 2001, LKF 014/993350, MRID 46387803, Unpublished.

SPONSOR: LG Chemical Ltd./Research Park Biotech Research Institute 1, 104-1, Moonji-dong, Yusong-Gu, Taejon, 305-380, Korea

EXECUTIVE SUMMARY: In a 90-day oral toxicity study (MRID 46387803), Ethaboxam (LGC-30473, 98% a.i.) was administered to four beagle dogs/sex/dose in a capsule daily at concentrations of 0, 15, 40, or 100 mg/kg/day.

There were no differences between the controls and treated groups in food and water consumption, ophthalmology, and urinalysis parameters that were considered toxicologically significant. There were three premature sacrifices (40 and 100 mg/kg/day groups) done for humane reasons, one male dog had meningitis and two females suffered from an anemic condition at necropsy. There were no clinical signs of toxicity noted for the surviving beagle dogs.

Treated dogs showed increases in absolute and relative (adjusted for body weight) liver weights in the 40 and 100 mg/kg/day groups of both sexes. These changes were associated with the microscopic finding of hepatocyte hypertrophy. A slight involution/atrophy of the thymus and extramedullary hematopoiesis in the spleen were detected in one dog of each sex in the 100 mg/kg/day group and one female in the 40 mg/kg/day group.

At termination, the treated male dogs had body weights comparable with controls while there was a 10 to 15% reduction in body weight of the female dogs. The body weight gain of the females was correspondingly reduced in all groups (62%, 52% and 41% of control levels in the 15, 40, and 100 mg/kg/day groups, respectively).

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The LOAEL for females is 15 mg/kg/day based on reduced body weight and body weight gain and the LOAEL for males is not determined. The NOAEL for males is 100 mg/kg/day and the NOAEL for females is not determined.

The 90-day oral toxicity study in dogs is **Acceptable/Guideline** and satisfies the guideline requirement (OPPTS 870.3150; OECD 409) for a 90-day oral toxicity study in dogs.

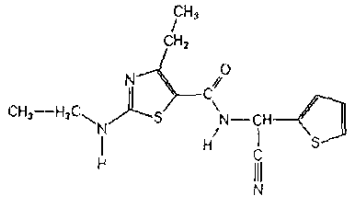
COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Data Flagging statements were provided.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material: LGC-30473

Description:	white powder
Lot/Batch #:	P980622
Purity:	99%
Compound Stability:	N/A
CAS # if TGAI:	162650-77-3
Structure:	



2. Vehicle and/or positive control: Capsule

3. Test animals:

Species:	Dog	
Strain:	Beagle	
Age/weight at study initiation:	Age: between 21 and 26 weeks old. Weight: between 7.7 and 10.7 kg (gender not specified).	
Source:	Cambell Farms, Cambridgeshire, U.K.	
Housing:	Two dogs in a custom designed dog pen according to United Kingdom Home Office Code of Practice for the Housing and Care of Animals used on Scientific Procedures. Each pen had a floor area of 4.5 m^2.	
Diet:	Pelleted standard dry diet (Diet A)	
Water:	City water	
Environmental conditions:	**Temperature:**	15 - 22°C
	Humidity:	NA
	Air changes:	10 times/hour
	Photoperiod:	12 hrs dark/ 12 hrs light (0700 to 1900)
Acclimation period:	At least 5 weeks	

B. STUDY DESIGN:

1. In life dates: Start: June 30, 1999; End: September 29, 1999

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2. **Animal assignment:** Animals were randomly assigned to the test groups noted in Table 1 by a pseudo-random body weight stratification procedure.

TABLE 1: Study design [a]

Test group	Dose to animal (mg/kg/day)	# Males	# Females
Control	0	4	4
1	15	4	4
2	40	4	4
3	100	4	4

[a] Data from p. 14, MRID 46387803.

3. **Dose selection rationale:** Not available in the report.

4. **Capsules (preparation, administration and analysis):** LGC-30473 was administered orally using Tor-pac, size 30 x 15 mm gelatin capsules. Individual doses were prepared weekly by dispensing the appropriate quantity of LGC-30473 into a gelatin capsule. The prepared capsules were stored at 4°C in the dark prior to use. LGC-30473 was administered orally at the same time each day (before noon), 7 days/week for 13 weeks; control dogs received an empty gelatin capsule. No analysis data were reported. Compound intake is summarized in Table 1.

5. **Statistics**: Statistical analyses were conducted on food consumption, body weight gain, clinical pathology, and organ weight data. The homogeneity of variance between treatment groups was performed by Bartlett's test. If no significant heterogeneity was detected; a one-way analysis of variance was carried out. If significant heterogeneity of variance was present, the Kruskal and Wallis method was used. These were followed by the appropriate Student's *t*-test or Williams' test. For incidence data, the Fisher Exact test was applied. Statistical significance was set at $p \leq 0.05$.

C. METHODS:

1. Observations:

1a. Cageside observations: Animals were inspected at regular intervals each working day for signs of toxicity and mortality.

1b. Clinical examinations: Clinical examinations (not specified) were conducted along with the cageside observations.

2. **Body weight:** Animals were weighed prior to treatment initiation, weekly throughout the study period, and on the day of necropsy.

3. **Food consumption and compound intake:** 400 g pelleted standard dry diet (Diet A) was given to each animal every day (one hour after dosing); remaining food was weighed after 24 hours. Food consumption for each animal was determined prior to treatment initiation, then daily throughout the study and on the last day of the administration period. The test material was administered in capsules.

4. **Water consumption:** Water was available to animals *ad libitum* at all times except when urine collection was performed. Water consumption for each animal was not measured.

5. **Ophthalmoscopic examination:** The eyes of each animal were examined once before treatment initiation and during Week 13 of the study. Mydriasis was induced with 1% tropicamide ophthalmic solution. Eyes were examined by a binocular indirect ophthalmoscope.

6. **Hematology and clinical chemistry:** Fasting blood samples were collected from the jugular vein of each animal prior to treatment and at Weeks 6, 11, and 13 of administration for hematology and clinical chemistry. The CHECKED (X) parameters were examined.

   a. **Hematology:**

X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpuscular HGB conc.(MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpuscular volume (MCV)*
X	Platelet count*	X	Reticulocyte count
-	Blood clotting measurements*	X	Erythrocyte sedimentation rate (ESR)
X	(Thromboplastin time)		
-	(Clotting time)		
X	(Prothrombin time)		

* Recommended for 90-day oral non-rodent studies based on Guideline 870.3150

- Not examined

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b. Clinical chemistry:

	ELECTROLYTES		OTHER
X	Calcium*	X	Albumin*
X	Chloride*	X	Creatinine*
-	Magnesium	X	Urea nitrogen*
X	Phosphorus*	X	Total Cholesterol*
X	Potassium*	X	Globulins
X	Sodium*	X	Glucose*
	ENZYMES (more than 2 hepatic enzymes suggested)*	X	Total bilirubin*
X	Alkaline phosphatase (ALK)*	X	Total protein (TP)*
-	Cholinesterase (ChE)	-	Triglycerides
-	Glutamate dehydrogenase	X	Serum protein electrophoresis
-	Lactic acid dehydrogenase (LDH)	X	Albumin/globulin (A/G) ratio
X	Alanine aminotransferase (also SGPT)*	X	Creatine phosphokinase
X	Aspartate aminotransferase (also SGOT)*	X	Ornithine carbamoyl transferase
-	Sorbitol dehydrogenase*		
X	Gamma glutamyl transferase (GGT)*		

* Recommended for subchronic non-rodent studies based on Guideline 870.3150

- Not examined

7. **Urinalysis:** Overnight urine samples were collected from all animals once prior to the treatment and during Weeks of 6 and 13. The CHECKED (X) parameters were examined.

X	Appearance*	X	Glucose*
X	Volume*	X	Ketones
X	Specific gravity /osmolality*	X	Bilirubin
X	pH*	X	Blood /blood cells*
X	Sediment (microscopic)	-	Nitrate
X	Protein*		

* Recommended for subchronic studies based on Guideline 870.3150

- Not examined

8. **Sacrifice and pathology:** Animals were fasted overnight prior to sacrifice by an intravenous injection of "Euthatal" followed by exsanguination. All sacrificed animals were subjected to gross pathological examination. The CHECKED (X) tissues were examined histologically from each animal. In addition, the (XX) organs were weighed.

   Bone marrow smears obtained from sternal puncture were air-dried and fixed in methanol by the Romanosky procedure. Eyes with optic nerve attached were fixed in Davidson's fluid; testes and epididymides were initially fixed in Bouin's fluid, and then stored in 70% I.M.S solution.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
-	Tongue	X	Aorta, thoracic*	XX	Brain*+
X	Salivary glands*	XX	Heart*+	X	Peripheral nerve*
-	Esophagus*			X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	X	Pituitary*
X	Duodenum*	X	Spleen*+	X	Eyes (optic nerve)*
X	Jejunum*	X	Thymus*+		GLANDULAR
X	Ileum*			XX	Adrenal gland*+
X	Cecum*		UROGENITAL		
X	Colon*	XX	Kidneys*+	XX	Parathyroid*+
X	Rectum*	X	Urinary bladder*	XX	Thyroid*+
XX	Liver*+	XX	Testes*+		OTHER
XX	Gall bladder*+	X	Epididymides*+	X	Bone (sternum and/or femur)
X	Pancreas*	X	Prostate*	X	Skeletal muscle
	RESPIRATORY	XX	Ovaries*+	X	Skin*
X	Trachea*	X	Uterus*+	X	All gross lesions and masses*
XX	Lung*	X	Mammary gland*		
-	Nose*				
X	Pharynx*				
X	Larynx*				

* Recommended for 90-day oral non-rodent studies based on Guideline 870.1350
+ Organ weight required for non-rodent studies.
- Not examined

II. RESULTS:

A. OBSERVATIONS:

1. **Clinical signs of toxicity:** No clinical signs of toxicity related to treatment with LGC-30473 were observed.

2. **Mortality:** Three beagle dogs were sacrificed for humane reasons: one female in the 40 mg/kg/day group at Week 10, one male in the 100 mg/kg/day group at Week 2, and one female in the 100 mg/kg/day group at Week 7. It was determined the male dog had meningitis and the two females suffered from an anemic condition.

B. BODY WEIGHT AND WEIGHT GAIN: Body weight and body weight gain data are shown in Table 2. At study termination, the body weights of males were comparable to that of controls. However, the body weight gains were decreased and ranged from 78 to 81% of the control in the 40 and 100 mg/kg/day groups. The body weights for females in the 40 and 100 mg/kg/day groups were decreased to 87 and 83% of control, respectively, starting at Week 6 and remained similarly decreased through the remainder of the study and was 90% of control in the 15 mg/kg/day group at Week 13. The body weight gain for females was reduced 62, 52, and 41% of controls in the 15, 40, and 100 mg/kg/day groups, respectively.

TABLE 2. Body weight and body weight gain in dogs during 90 days of treatment with LGC-30473 [a]						
Dose group, (mg/kg/day)	Body weight, kg (% of control)[b]				Total weight gain	
	Week 0	Week 1	Week 6	Week 13	Kg	% of control [b]
Males						
0	9.2	9.4	10.9	12.4	3.2 ± 0.66	–
15	9.5	9.9	11.3 (104)	12.4 (100)	2.9 ± 0.70	91
40	9.1	9.6	10.8 (99)	11.8 (95)	2.6 ± 0.46	81
100	9.2	9.6	10.6 (97)	11.6 (94)	2.5 ± 0.32	78
Females						
0	9.2	9.7	10.9	12.0	2.9 ± 0.26	–
15	9.0	9.3	10.2 (94)	10.8 (90)	1.8 ± 0.74	62
40	8.6	8.6	9.5 (87)	10.3 (86)	1.5 ± 0.51	52*
100	8.8	9.0	9.1 (83)	10.2 (85)	1.2 ± 1.04	41*

[a] Data from pages 44 and 125-126, MRID 46387803.
[b] Percent of control, mean of weight gain and S.D. calculated by the reviewer.
* $p<0.05$

C. FOOD CONSUMPTION AND COMPOUND INTAKE:

1. **Food consumption:** Only female dogs in the 100 mg/kg/day group exhibited statistically lower (~15%) food consumption. There was no effect on the males.

2. **Water consumption:** Water consumption was not reported.

3. **Compound consumption:** Compound consumption is shown in Table 1.

4. **Food efficiency:** Food efficiency was not reported.

D. OPHTHALMOSCOPIC EXAMINATION: No treatment related lesions were observed.

E. BLOOD ANALYSES:

1. **Hematology:** In males of the 100 mg/kg/day group, hemoglobin was statistically decreased at Week 6 (Table 4). Erythrocyte and hematocrit values were similarly affected during Weeks 6 and 11, (87% [$p<0.05$] and 90-88% ($p<0.05$ or 0.01) of control, respectively). There were sporadic changes in the white blood cell populations in treated dogs, but were not considered treatment related. The other hematological parameters were comparable to those of controls.

   In females, there was a reduction of hemoglobin concentration in the 100 mg/kg/day group that ranged from 83% to 89% of controls starting in Week 6 to termination. Erythrocyte and hematocrit values were decreased ranging from 87% to 81% and 88% to 83%, respectively of the controls from Weeks 6 until the end of the study. There were no other hematological parameters that could be directly related to the treatment with LGC-30473.

TABLE 4. Hematology findings in dogs receiving LGC-30473 orally for 90 days[a]				
Parameters	Group and dose, mg/kg/day[b]			
	0	15	40	100
Males				
Hemoglobin (g/dL)				
Week 0	11.9 ± 1.11	11.6 ± 0.95 (97)	12.5 ± 0.88 (105)	12.2 ± 0.52 (103)
Week 6	14.3 ± 0.06	13.8 ± 0.51 (97)	13.4 ± 0.77 ((94)	13.0 ± 1.16 (91)*
Week 11	14.2 ± 0.41	13.8 ± 0.52 (97)	13.3 ± 2.10 (94)	12.8 ± 1.26 (90)
Week 13	14.9 ± 1.04	13.3 ± 0.78 (89)	13.5 ± 1.92 (91)	14.4 (97)[c]
Erythrocyte (10^{12}/L)				
Week 0	5.58 ± 0.375	5.32 ± 0.643	5.64 ± 0.369	5.57 ± 0.280
Week 6	6.56 ± 0.256	6.20 ± 0.431 ((95)	5.91 ± 0.289 (90)	5.73 ± 0.682 (87)*
Week 11	6.51 ± 0.128	6.11 ± 0.153 (94)	5.84 ± 0.885 (90)	5.66 ± 0.758 (87)*
Week 13	6.93 ± 0.435	6.00 ± 0.363 (87)	6.04 ± 0.846 (87)	6.43 (93)
Hematocrit (v/v)				
Week 0	0.370 ± 0.0291	0.356 ± 0.0290	0.381 ± 0.0274	0.379 ± 0.0154
Week 6	0.473 ± 0.0038	0.456 ± 0.0210 (96)	0.441 ± 0.022 (93)	0.424 ± 0.0374 (90)*
Week 11	0.441 ± 0.0092	0.419 ± 0.016 (89)	0.403 ± 0.0608 (91)	0.392 ± 0.0388 (88)
Week 13	0.467 ± 0.0296	0.415 ± 0.0284 (89)	0.415 ± 0.0564 (89)	0.440 (94)
Reticulocyte count (%)				
Week 0	1.31 ± 0.533	1.58 ± 0.332	1.05 ± 0.178	1.18 ± 0.415 (90)
Week 6	1.08 ± 0.102	1.20 ± 0.370	1.05 ± 0.557	1.02 ± 0.318 (94)
Week 11	0.91 ± 0269	0.89 ± 0.381	0.77 ± 0.221	1.07 ± 0.899 (118)
Week 13	1.15 ± 0.285	1.17 ± 0.442	0.87 ± 0.399	0.95 (83)
Females				
Hemoglobin (g/dL)				
Week 0	13.2 ± 0.66	13.4 ± 0.85	13.7 ± 1.50	12.8 ± 0.56
Week 6	15.1 ± 0.50	14.5 ± 0.45 (96)	14.3 ± 1.60 (95)	13.1 ± 1.66 (87)*
Week 11	15.4 ± 1.33	14.7 ± 0.39 (95)	13.8 ± 1.65 (90)	12.8 ± 0.66 (83)*
Week 13	15.2 ± 0.74	15.0 ± 0.32 (99)	14.1 ± 1.51 (93)	13.5 ± 0.53 (89)*
Erythrocyte (10^{12}/L)				
Week 0	5.92 ± 0.248	6.18 ± 0.166	6.08 ± 0.512	5.81 ± 0.304
Week 6	6.69 ± 0.175	6.56 ± 0.324 (98)	6.33 ± 0.567 (95)	5.81 ± 0.791 (87)*
Week 11	6.90 ± 0.509	6.65 ± 0.320 (96)	6.16 ± 0.496 (89)	5.61 ± 0.351 (81)**
Week 13	6.87 ± 0.211	6.83 ± 0.116 (99)	6.34 ± 0.403 (92)*	5.94 ± 0.251 (86)**
Hematocrit (v/v)				
Week 0	0.407 ± 0.0188	0.414 ± 0.0228	0.420 ± 0.0461	0.395 ± 0.0136
Week 6	0.495 ± 0.0172	0.476 ± 0.0150 (96)	0.472 ± 0.0517 (95)	0.430 ± 0.0577 (87)*
Week 11	0.478 ± 0.0383	0.450 ± 0.0168 (94)	0.424 ± 0.0495 (89)	0.395 ± 0.0143 (83)**
Week 13	0.472 ± 0.0199	0.465 ± 0.0118 (99)	0.434 ± 0.0404 (92)	0.416 ± 0.0220 (88)*
Reticulocyte count (%)				
Week 0	1.32 ± 0.227	1.40 ± 0.567	0.93 ± 0.242	0.97 ± 0.294 (73)
Week 6	1.29 ± 0.303	1.17 ± 0.336	0.54 ± 0.259 (42)*	1.09 ± 0.290 (84)*
Week 11	1.08 ± 0.396	1.14 ± 0.527	0.53 ± 0.211 (49)	0.64 ± 0.261 (59)
Week 13	1.20 ± 0.158	1.22 ± 0.486	0.66 ± 0.115 (55)	1.01 ± 0.689 (84)

[a] Data from pages 46-63, MRID 46387803.
[b] Percent of control in the parenthesis, calculated by the reviewer.
[c] No SD was provided (two samples)
* $p<0.05$, ** $p<0.01$, *** $p<0.001$

2. **Clinical chemistry:** The cholesterol was increased 142 to 206% of controls in males that received ≥ 15 mg/kg/day LGC 30473. The cholesterol of females was increased 112-153% of controls (Table 5).

TABLE 5. Clinical chemistry findings in dogs receiving LGC-30473 orally for 90 days[a,b]				
Organ	Group and dose, mg/kg/day			
	0	15	40	100
Males				
Cholesterol (mM/L)				
Week 0	2.95 ± 0.443	3.21 ± 0.401	3.08 ± 0.299	3.20 ± 0.699
Week 6	3.35 ± 0.554	4.33 ± 0.901 (129)	4.05 ± 0.290 (121)	6.41 ± 3.036 (191)*
Week 13	3.07 ± 0.688	4.38 ± 1.021 (143)	4.37 ± 0.324 (142)	6.33 ± 2.825 (206)**
Females				
Cholesterol (mM/L)				
Week 0	2.91 ± 0.375	2.77 ± 0.473	3.02 ± 0.539	2.64 ± 0.617
Week 6	2.95 ± 0.538	2.82 ± 0.479 (96)	3.44 ± 0.782 (117)	4.97 ± 2.369 (168)
Week 13	2.74 ± 0.493	3.08 ± 0.412 (112)	3.44 ± 0.640 (126)	4.18 ± 1.780 (153)

[a] Data from pages 64-81, MRID 46387803.
[b] Number in parenthesis represents % of control value, calculated by reviewer.
* $p<0.05$, ** $p<0.01$

F. URINALYSIS: There were no abnormal findings related to the treatment with LGC-30473.

G. SACRIFICE AND PATHOLOGY:

1. **Organ weight:** Although not clearly dose related, male and female dogs that received LGC-30473 at 40 and 100 mg/kg/day showed increases in absolute and relative liver weights. In addition, male dogs showed decreases in absolute thymus weight (Table 6). In females, the absolute thymus weight was decreased to 43% of control at the highest dose.

TABLE 6. Mean absolute (g) and relative (to body weight, %) organ weight of dogs receiving LGC-30473 for 90 days[a,b]

	Group and dose, mg/kg/day			
	0	15	40	100
Males				
Body wt. *(kg)*	12.4	12.4	11.7	11.2
Liver:				
- Absolute	387 ± 41	432 ± 19 (112)	486 ± 44 (126)**	532 ± 58 (137)**
- Relative	3.13 ± 0.04	3.50 ± 0.29 (112)	4.17 ± 0.22 (133)**	4.80 ± 0.56 (153)**
Thymus:				
- Absolute	16.2 ± 4.19	13.03 ± 7.10 (80)	13.45 ± 1.59 (83)	10.28 ± 3.86 (63)
- Relative	0.1304 ± 0.0287	0.1023 ± 0.0480 (78)	0.1161 ± 0.0172 (89)	0.0926 ± 0.0334 (71)
Females				
Body wt. *(kg)*	12.0	10.7	10.0	9.3
Liver:				
- Absolute	370 ± 29	376 ± 52 (102)	430 ± 70 (116)**	427 ± 53 (115)**
- Relative	3.12 ± 0.31	3.52 ± 0.15 (113)	4.39 ± 0.79 (141)*	4.68 ± 0.61 (150)**
Thymus:				
- Absolute	12.03 ± 3.86	11.82 ± 3.60 (98)	10.99 ± 4.92(91)	5.16 ± 4.85 (43)
- Relative	0.1020 ± 0.0354	0.1092 ± 0.0211 (107)	0.1103 ± 0.0409((108)	0.0533 ± 0.0454 (52)

[a] Data from pages 94-99, MIRID 46387803.
[b] Percent of control, ANOVA, and Dunnett's test conducted by the reviewer
* $p<0.05$, ** $p<0.01$

2. **Gross pathology:** There were no abnormal gross lesions in the treated dogs that could be related to treatment, except enlargement of the liver.

3. **Microscopic pathology:** In males, there was a dose-related increase in liver hepatocyte hypertrophy in 1/4, 3/4, and 3/3 dogs that received 10, 40, or100 mg/kg/day, respectively. A slight involution/atrophy of the thymus and extramedullary hematopoiesis in the spleen were detected in 1/3 male dogs in the 100 mg/kg/day group. In females, there was also a dose related increase in liver hepatocyte hypertrophy in 3/3 and 3/3 dogs that received 40 and 100 mg/kg/day groups, respectively. Moderate involution/atrophy of the thymus was also found in 2/3 females that received 100 mg/kg/day. In addition, extramedullary hematopoiesis in the spleen was detected in one female each from the 40 and 100 mg/kg/day groups.

III. DISCUSSION AND CONCLUSIONS:

A.INVESTIGATORS' CONCLUSIONS: There were three dogs (one male and one female at 100 mg/kg/day and one female at 40 mg/kg/day) that were sacrificed prematurely for humane reasons. The male dog was diagnosed with meningitis and the two female dogs suffered from anemic conditions. These findings were considered unrelated to treatment. Necropsy showed the male dog had histopathological changes consistent with thymic involution/atrophy and hepatocyte hypertrophy. The female dogs showed changes consistent with hemolysis with a regenerative response in the spleen and bone marrow. For the surviving dogs, slight reductions in hemoglobin, hematocrit, and erythrocyte counts were found in the 100 mg/kg/day group and primarily in males treated at 40mg/kg/day throughout the study. These changes were also seen in males treated with 15 mg/kg/day during Week 13.

W3

Both male and female dogs showed a dose related reduction in body weight gain at termination. There were marked differences among the female groups especially for the 100 mg/kg/day group that was associated with reduced food intake. There was a marginal reduction in body weight gain in males at 15 mg/kg/day.

In addition, adaptive responses to treatment with LGC-30473 were seen in the liver. Hepatocyte hypertrophy was found in all groups except at 15 mg/kg/day group, this was associated with increased liver weight (all groups) and enlargement (at 40 and 100 mg/kg/groups)of the liver. Increasing levels of cholesterol were found in the blood at all dose levels except the females at 15 mg/kg/day group.

The author concluded that a NOAEL was not identified principally due to impairment of body weight gain observed for three of the four females at 15 mg/kg/day; however, dose levels for a subsequent 52-week study (LKF/015) were established at 0, 5, 10, and 30 mg/kg/day.

B. **REVIEWER COMMENTS:** There were no differences between the controls and the treated groups in food and water consumption, ophthalmology, and urinalysis parameters that were considered toxicologically significant. There were three premature sacrifices (one of each sex at 100 mg/kg/day and one female at 40 mg/kg/day group) done for humane reasons, one male dog had meningitis and two females dogs suffered from an anemic condition at necropsy. There were no clinical signs of toxicity noted for the surviving beagle dogs.

Hematology parameters were not adversely affected by treatment.

Treated dogs showed increases in absolute and relative (to body weight) liver weights in the 40 and 100 mg/kg/day groups of both sexes which were associated with microscopic findings of hepatocyte hypertrophy. Slight involution/atrophy of the thymus and extramedullary hematopoiesis in the spleen were found in one dog of each sex in the 100 mg/kg/groups and one female in the 40 mg/kg/day group.

Throughout the study treated male beagle dogs had body weights comparable with the controls; females showed decreases of 10 to 15% at all doses at 13 weeks. The body weight gain was decreased to 81% and 78% of controls in males at 40 and 100 mg/kg/day, respectively. The body weight gain of females was severely reduced in all groups, 62%, 52% and 41% of control for 15, 40, and 100 mg/kg/day groups, respectively.

The LOAEL for females is 15 mg/kg/day based on reduced body weight and body weight gain and the LOAEL for males is not determined. The NOAEL for males is 100 mg/kg/day and the NOAEL for females is not determined.

C. **STUDY DEFICIENCIES:** There were no serious deficiencies that would invalidate the study results.

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